EDITORIAL ARTICLES.

LANZ ON THE THYREOID QUESTION.[1]

IN an elaborate essay upon this subject, Lanz, of Bern, states that to Schiff is due the credit of first demonstrating by experiments upon animals that the thyreoid is not, as had been hitherto supposed, an organ of no importance. Kocher's reports of the results of thyreoidectomy in man, presented before the German Surgical Congress, at Berlin, in 1883, have excited such general attention to this subject that from that time on the thyreoid question has been a subject of lively discussion; and Horsley, in 1891, in his thorough analysis of the subject, has removed the least doubt that the thyreoid gland has a specific and very important function.

In the year 1873, Gull described a cretinoid affection, which later (1877) Ord designated by the name myxœdema. Ord observed in this new disease the degeneration of the thyreoid gland, which could not be etiologically associated with the disease. Charcot, in 1881, described the disease as *cachexie pachydermique*, but did not go into the pathology of the malady.

The similarity between the symptoms described by Kocher as following extirpation of the thyreoid and the disease of myxœdema, first observed in England, occurred to Felix Siemon as being a very striking one, and led him to suppose that the latter might be due to some destruction of the thyreoid. That the cause of the myxœdematous systemic changes were to be sought for in the thyreoid was the conclusion reached by the "myxœdema commission" in 1888, because, without exception, in every one of the several hundred cases examined, the only constant change found in the body was an atrophy or degeneration of the thyreoid gland.

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[1] Lanz: Zur Schilddrüsenfrage, Sammlung klinische Vorträge, No. 98, 1894.

The differences in the symptoms of myxœdema and cachexia thyreopriva, to which Bircher has called attention, consist only in the different manners in which the thyreoid becomes degenerated. The experimental observations made by Schiff, Horsley, and Fuhr confirm the clinical observations of Kocher and Reverdin. Horsley has removed the thyreoid from apes, and produced a disease similar to the cachexia thyreopriva.

The similarity between goitre and cretinism has been known for a long time. Virchow expressed himself that endemic cretinism did not exist in any single part of the world where endemic goitre was not also found. The production of the operative cachexia has established the connection between the two diseases, and Kocher was the first to declare that the cachexia thyreopriva and the real cretinism are one and the same affection, be the latter due to goitrous degeneration or to the absence of the thyreoid gland.

As soon as the pathological identity of operative cachexia, myxœdema, and real cretinism were recognized, it became evident that for the general designation of the disease, as it appears in connection with degeneration or absence of the thyreoid gland, the name cachexia thyreoidea, suggested by Kocher, had best be adopted, not only for the myxœdema, but also for the operative form of the disease. The first, together with its infantile form—cretinism—may be called cachexia thyreopriva, and the second—the active form—may be called cachexia thyreoidectomica. The expression myxœdema should be entirely dropped, as it is only a symptom, and not the real disease. It certainly would not be appropriate to designate the disease-process of cirrhosis as ascites.

As has already been stated, Horsley, in 1891, collected and sifted all of the evidence which had accumulated up until that time. Lanz has made it the object of his paper to give a *résumé* of the subject, and bring up to date a topic which has received so much scattered attention during these few past years. He takes up the subject where Horsley left off in 1891, and assumes from the beginning that the Englishman's work is well known, as well as that of Hofmeister,[1] which appeared about the same time.

Development of the Thyreoid.—It is agreed that the epithelium of the thyreoid gland develops primarily from the epithelium of the wall of the neck, at the level of the second branchial arch. The publication of Wölfler[2] has done much to advance our knowledge of the embryology of the thyreoid; and more recently are the publications of Dohrn[3] and His.[4] According to His, a cavity is shut off by the union of the two segments of the hyoid bone, from which develops an epithelial alveolus. This epithelial inclusion or sac is that part which becomes the odd or middle lobe of the thyreoid, which, for a long time during the process of its development, communicates at the root of the tongue with the epithelium of that organ. The outlet canal, which begins at about the thyreoid cartilage, and which eventually becomes obliterated, is the so-called ductus thyreoglossus, and the remains of its mouth can be seen in the foramen cæcum of the tongue. The origin of the two lateral portions of the thyreoid, which eventually become fused to the middle portion, as Born first pointed out, is not as yet explained. Born believes that they originate from the fourth branchial pouch. His and Bemmelen believe that the origin must be sought not only in this but also in the primary parts of the floor of the mouth, as is the case with the middle lobe, which becomes shut off from the chief cavity in the process of development. The central piece later becomes united with the lateral parts of the gland. His has observed in an embryo 9.1 millimetres long that, before this amalgamation takes place, the middle portion gives off two lateral horns which may take part in the formation of the lateral lobes. In an human embryo sixteen millimetres long he observed that the hyoid bone projected into the thyreoglossal tract in such a way that its upper portion began in front of the body of the hyoid bone, and the lower portion began below the hyoid bone. This is explained by the fact that the accessory thyreoids and cysts arising from the upper portion of the *ductus thyreoglossus* lie in front of the hyoid bone, though the *processus pyramidalis* is inserted behind the same. Nevertheless, Kanthack[1] denies that there is any embryological connection between the foramen cæcum and the thyreoid gland.

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[1] Fortschritte der Medicin, Nr. 3 u. 4, 1892.

[2] Entwicklung und Bau der Schilddrüse, Reimer, 1880.

[3] Entwicklung und Bedeutung der Glandula Thyreoidea, Mittheilungen der Zoologie, L.Station in Neapel, 1886.

[4] Der Tractus Thyreoglossus und seine Beziehungen zum Zungenbein, Arch. für Anat. u. Physiol., 1891, S. 26.

Comparative Anatomy.—Dohrn agrees with W. Müller that the thyreoid of the ammocœtes is identical with the hypobranchial ridge of the tunicatæ and the amphioxus, though there are many important differences. Müller was the first to show that the hypobranchial ridge of the tunicatæ is a homologue of the same structure in the amphioxus. Rolph, Langerhans, Rohon, and Dohrn have made a special study of the same, and regard it as originating by an inclusion from the middle cavity of the gill-region.

In the ammocœtes and the larva of the petromyzon the communication of the thyreoid with the lumen of the throat is at first very large, but later becomes contracted so that the gland has the appearance of a diverticulum of the œsophagus. In the grown petromyzon the gland becomes shut off from the throat-cavity, and follicles develop just as in other vertebrates.

In the higher order of cartilaginous fishes the separation of the thyreoid from the digestive canal is complete. It lies as a single organ beneath the symphysis of the lower jaw, exactly in the middle line, at the bifurcation of the trunk of the gill artery, and between this and the capula of the arch of the hyoid bone. In the bony fishes there are a pair of thyreoid glands developed during the postfœtal period which lie at the posterior ends of the first branchial arch. So in the amphibiæ and birds there are a pair of thyreoids which are entirely shut off from the inside of the throat, and which come finally to lie more upon the ventral aspect of the trachea or larynx.

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[1] The thyreoglossal duct, Journal of Anatomy and Physiology, Vol. XXV, P. II, p. 155.

It is the general rule among the mammaliæ to have a thyreoid of two or three lobes. In vertebrates are always found accessory thyreoids near the main gland. Van Bemmelen[1] has discovered in embryos epithelial derivatives behind the branchial clefts of the ventral aspect of the wall of the throat, which he has designated as "suprapericardial bodies." De Meuron has described homologous structures which he has observed in lizards, and which he has called *thyreoides accessoires*, because of the similarity of the structure of the two bodies, and because these bodies become fused together in the mammalia by the central lobe. In mammals, besides the chief lateral lobes, many writers have described accessory lateral lobules. These structures evidently arise from the same source as the gland proper.

Histology.—The thyreoid gland has in the beginning the character of a real gland, but which becomes lost. It is divided into lobules, by a connective-tissue frame-work, and is exceedingly rich in its blood-supply. In fishes and amphibians it contains large, bladder-like follicles lined with epithelium. Besides these, the thyreoids of the higher vertebrates contain also cylindrical tubules which divide and subdivide, but which finally terminate in separate single alveoli. The mature gland of the mammal presents a convolution of circularly-enclosed glandular vesicles which are surrounded by a connective-tissue envelope and vascular net-work.

Wagner was the first to observe that after the extirpation of one lobe of the thyreoid the other hypertrophied; and thereby this organ was demonstrated to respond to the same laws as govern other glandular structures.

In the same way have the experiments of Ribbert shown the analogy to other glands, in the regeneration of its parenchymatous elements, by a proliferation of the epithelium of the old alveoli and the formation of sprouts which grow into the connective-tissue, and there arrange themselves into small groups, secrete colloid material, and become changed into colloid-containing vessels lined with epithelium.

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[1] Anatom. Anzeiger, 1889, No. 13.

Pathological Anatomy.—The subject of thyreoid cachexia, since Horsley's work, has been advanced by the studies of Langerhans and his students.

The etiology of this affection, associated with degeneration of the thyreoid, is still not well understood.

Myxœdema seems to be associated with an inflammatory process in the thyreoid, which begins with a round-cell infiltration of the thyreoid, and later results in a shrinking of the gland, which may be compared with cirrhosis of the liver. In a section of myxœdematous thyreoid is seen the inflammatory infiltration. The acini seem farther apart than normal, and in some of the groups of inflammatory cells but a few epithelial cells can be seen representing the remains of acini. In some sections no sign of epithelium can be found. The vessels of the gland present greatly-thickened walls from endarteritic changes, and the smaller vessels become entirely obliterated. Atrophy of the epithelium is observed in the skin, the sebaceous follicles are enlarged, the hair-follicles are atrophic, and at their opening is usually found a broken and swollen hair. In the subcutaneous tissue, instead of the normal trabeculæ, are found only delicate fibrillar bundles, and the fat-cells are smaller than normal. Throughout the brain, liver, kidneys, lungs, and muscles are found connective-tissue growths associated with marked endarteritis and periarteritic changes.

The increased amount of mucin in the skin was first observed by Charles in such cachectic persons; and Halliburton has observed the same in apes after thyreodectomy.

But little has been accomplished in the study of goitre. Investigations which have been carried out in large numbers of cases lead to the conclusion that the condition of the soil is answerable for the occurrence of the disease. The only constant factor by which the soil is known to give rise to the disease is the drinking water. Kocher[1] found, by examining the school children of every family which used from common wells in the Lauterbrunnenthal region, that there were certain individuals without goitre, but that all of these persons who were not afflicted with the disease obtained their water from a certain well which the diseased persons did not use. The persons who confined themselves strictly to this well remained free from thyreoid enlargement. St. Lager observed that the people in districts where rain-water was used did not contract the disease. It is not known what substance in the water causes goitre; nor have any particular geological conditions been definitely fixed upon as having an etiological bearing. The same kind of geological formation may in one place produce an abundance of the disease, and another place may be entirely free. Numerous observations have been made to show that it is not alone the mineral character of the locality, but much more the organic elements of the soil which are of etiological importance. Kocher has cited Humboldt as the first to classify goitre and cretinism among infectious diseases. Investigations have been made by Klebs, Bircher, and Tavel into the waters of goitrous regions to discover some organic cause for the disease. Tavel found in goitrous water thirty-three different varieties of organisms. The waters in the same region which did not produce goitre contained but nine kinds. It may be concluded from this that the particular waters which give rise to goitre are rich in organic matter. Lanz has made repeated inoculations from goitrous thyreoids with negative results.

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[1] Deutsche Zeitschrift für Chirurgie; Festschrift für Professor Thiersch, 1892.

Horsley has presented the following observations as bearing upon the question of cachexia: Zesas observed that in cats and dogs the spleen became hypertrophied after removal of the thyreoid. Sanguirico and Canalis observed in dogs marked anæmia and cerebral œdema, congestion of the mesenteric vessels, swelling of the liver, and in one case punctiform hæmorrhages of the intestine. Hyperæmia of the brain has been found by many observers. Albertoni and Tizzoni found degenerated islands in the peripheral nerves. Rogowitsch discovered a change characterized by destruction of the ganglion cells as a result of degeneration of the nuclei, vacuolization, degeneration of the protoplasm, and round-cell infiltration of the tissue. He observed also a colloid degeneration of the cells of the hypophysis. Schwartz was not able to find these changes, but Löwenthal observed the formation of vacuoles and atrophy of the large pyramidal cells in the cortical centres of the lower extremities of a dog.

Since these publications of Horsley, the following observations have been added to the literature:

Hofmeister did not find any vicarious hypertrophy of the spleen or thymus after thyreoidectomy in rabbits; in fact, the spleen was invariably smaller than in the control animals and showed no microscopic changes. The hypophysis was invariably enlarged 50 or 100 per cent. as compared with the control animals of the same litter. Hofmeister is inclined to believe with Virchow that there is a physiological relation between the thyreoid and the hypophysis. The embryology of this relation has been shown by Dohrn; and Rogowitsch and Stieda have made experimental demonstrations which corroborate his conclusions. Hofmeister found an increase in the size of the cells of that body. The same experiments showed a retarding of the development of the skeleton after thyreoidectomy. By exact comparative measurements of the operated and control animals from the same litter, a marked checking of the bony development was observed. The greatest differences were seen in the large long bones, the pelvis, and spinal vertebræ. The bones of the skull were the least retarded of any. There was always a marked retardation in the ossification of the epiphyseal line. These facts are in harmony with the observations in human pathology. True cretins are short in stature, and even in adults the epiphyses and synostoses are still cartilaginous, as has been shown by Dolega, Langerhans, and others. Bruns has published a case which, eighteen years before, had been subjected to thyreoidectomy, and which at the age of twenty-eight was not taller than a ten-year-old boy, the longitudinal growth of the body having remained stationary ever since the operation. Nauwerk, who had the opportunity of making an autopsy, found the epiphyseal lines in places still cartilaginous.

Hofmeister has found in the kidneys of such cases a peculiar change in the epithelium of the tubuli contorti. The ovaries are regularly the seat of a marked change, consisting in the simultaneous premature ripening of numerous follicles,—the follicular hypertrophy of Ziegler. The remaining organs, brain, cord, liver, stomach, intestine, suprarenal bodies, thymus, spleen, testicle, and epididymis, examined by Hofmeister, showed no changes. Another regular and striking change in the appearance of the animal, aside from its shortness, was the thickness and plumpness which it developed one month or six weeks after the operation. A less constant change was the coarseness of the hair, and the breaking off of the "feeling hairs" of the face.

Gley[1] showed that by simultaneous removal of both accessory thyreoids the symptoms of acute cachexia developed. In chronic cases he observed the falling out of hair and the formation of nodular thickenings in the skin.

Christiani[2] experimented upon rats, and observed also an acute cachexia after the operation.

Von Eiselsberg[3] made the same experiments upon sheep and goats as Hofmeister made upon rabbits.

Schönemann[4] examined in 112 cases the condition of the pituitary body in cases in which the thyreoid gland was in some manner degenerated. He came to the conclusion that there was no parallel between the weight of the thyreoid and the hypophysis, nor was he able to observe any compensatory hypertrophy of the hypophysis in cases of carcinoma or struma of the thyreoid. The histological examination of the pituitary body, however, showed that in struma thyreoidea there was very commonly certain changes in the former, which might not be regarded as compensatory or vicarious, but which occurred parallel with the degeneration of the thyreoid.

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[1] Comptes-rendus de la Société de Biologie, 1891, No. 37, Semaine médicale, 1892, No. 37, and Arch. de Physiologie.

[2] Arch. de Physiologie, 1893, No, 1.

[3] Centralb. für path. Anat. und allg. Pathologie, 1893, S. 353.

[4] Virchow's Archiv, Bd. 129, 1892. S. 310.

Boyce and Beadles report two cases of myxœdema and one of sporadic cretinism in which the enlarged hypophysis, in the absence or atrophic state of the thyreoid, was indeed shown to have assumed an increased activity of function.

The relation of the nervous system to cachexia thyreopriva has been described by Arthand and Magnon,[1] who have rehashed the old theory of Munk, and regarded the cachexia as due to a neuritis of the vagus nerve.

Langerhans and Kopp[2] have published two works upon the relation of the peripheral nervous system to the acute cachexia of the dog and to the more chronic cachexia of the ape and man, and its bearing upon cretinism. Langerhans found in the peripheral nerves, both in men and apes, after extirpation of the thyreoid, as well as in cretins, the following changes, sometimes single and sometimes combined, and involving both the trunks and the small muscular branches: (1) Thickening of the walls of the vessels, especially the capillaries; (2) dilatation of the lymph-spaces beneath the perineurium and in the endoneural connective tissue; (3) the appearance of peculiar cells, resembling œdematous cells of the endoneurium, and containing small vesicles (these cells were observed in the dilated lymph-channels); (4) patches of deposits of flat longitudinal fibrous bundles, associated with circumscribed dilatation of the peripheral lymph-channels, the latter containing the peculiar vacuolated cells; (5) isolated appearance of peculiar long spindles, having loose, concentric fibrous tissue about their periphery, and a centre of non-nucleated homogeneous material formed from the degenerated fibres.

Kopp found the ectasia of the lymph-spaces and the vesiculated cells in dogs.

Langerhans observes that the connection between these changes and the removal of the thyreoid or struma and cretinism have been seen by many investigators. Schultze and his student Trzebinsky have accurately described them. The latter found them in the brachial plexus in twenty-eight out of sixty-five cases.

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[1] Comptes-rendus de la Soc. de Biol., 1891, No. 26.

[2] Virch. Arch., Bd. 128, 1892, S. 290, ff.

The central nervous system of a dog suffering from cachexia thyreoidectomica was studied by Kopp, who found only a swelling of the axis cylinders.

Exact investigations of this point were made by De Quervain,[1] who examined the central nervous systems of an ape, cachectic dogs and cats, in connection with those of control animals. After passing the specimens through the various fixing, hardening, and staining processes, he came to the conclusion that, with the present known methods for studying nervous tissue, no constant changes could be found which could be positively declared as due to the disease of the thyreoid.

Kent's reports of the discovery of constant bacilli and cocci in the tissue of cachectic animals, Lanz does not regard as worthy of discussion.

Function of the Thyreoid.—Horsley has come to the conclusion that the best grounded of the theories concerning the function of the thyreoid is that which claims that the organ destroys or changes certain substances which circulate in the blood, and which have a harmful influence upon the general system. He also adds that the thyreoid secretes a substance which serves in the metabolism of the body.

As the metabolic process in cold-blooded animals is much slower than in the warm-blooded, Lanz has carried out a number of experiments by removing the thyreoids of the former at the zoölogical station at Naples. He employed fishes, amphibians, and reptiles in the course of his experiments.

The amphioxus he found too small for satisfactory experimenting. Experiments were made with the ammocœtes, the larva of the petromyzon, in which the thyreoid secretes externally and represents the transformation stage in which the organ becomes shut off from the throat cavity. The ammocœtes is such a delicate creature that none of the animals upon which he operated lived longer than thirty-six hours. The shark (*scillium catulus* and *S. canicula*) was next tried. The removal of the thyreoid from fifty sharks gave an almost completely negative result. They recovered quickly from the operation, and later on did not differ from the control fish, either in the swimming or general habits and appearance, though the shark responds very promptly to inoculation with tetanizing poisons. The total extirpation of the thyreoid and its accessory bodies diminished the strength and shortened the life of the sharks thus treated.

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[1] Virch. Arch., Bd. 133, 1803.

Bony fishes, which differ from the cartilaginous fishes in that they have no accessory thyreoids, do not survive the operation of thyreoidectomy.

Reptiles bear the operation well. Twelve lizards (*lacerta viridis*) gave negative results. These animals possess suprapericardial bodies which cannot be removed.

One of the most important points in Horsley's work is his demonstration of the parallelism between the general nourishment and the results of removal of the thyreoid. According to Horsley the reaction runs parallel with the variations in the food which the animal takes. "Those animals are affected the most which subsist entirely upon flesh, and those which are entirely herbivorous suffer the least, while the omnivorous animals are affected in a middle degree between the two." This observation shows that the thyreoid really plays a part in the metabolism of the body, and that there is a definite chemico-vital basis upon which to work out its function.

Gley and Christiani have found that it makes a very great difference whether the chief gland alone is removed or the accessory glands with it. While the simple extirpation of the chief gland caused no acute symptoms, fourteen out of sixteen rabbits, upon which was done a total extirpation, including the glandulæ paraparotideæ, perished with acute cachexia. On the second day dyspnœa and muscular weakness appeared. This was followed by paralysis of the extensors, spasms, opisthotonos, difficulty in walking, rise of temperature, and death, usually within the first week from a tetanic attack.[1]

Christiani[2] has performed a large number of thyreoidectomies upon rats, and has arrived at the following conclusions :

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[1] Arch. de Physiol., 1892, p. 81 ; Ibid., 1892, p. 135 ; Ibid., 1892, p. 311.

[2] Revue médicale de la Suisse romande, 1892, No. 11 ; Arch. de Biol., Janv., 1893 ; Arch. de Physiol., 1893, No. 1.

(1) Total thyreoidectomy causes death in the rat in the course of a few hours or after some days. Death is preceded by symptoms similar to those observed in other animals,—as the cat, for example,—muscular weakness, dyspnœa, stiffness of the extremities, and emaciation.

(2) In the many cases in which the animal survived, the excision was found not to be a total one, and the autopsy showed regenerated glandular elements.

(3) When the extirpated gland is implanted in the peritoneum the cachexia can be diminished, and the life of the animal preserved.

These fundamental principles have been demonstrated in the dog by Schiff, corroborated in the cat by Von Eiselsberg, and transferred to human pathology by Kocher, Bircher, and Horsley. Von Eiselsberg has made the demonstration that the thyreoid can be transplanted upon the peritoneum, and between the fascia and peritoneum, where it continues to live without becoming absorbed. He demonstrated that the cat did not perish after a total thyreoidectomy and such a transplantation, but the subsequent removal of the transplanted gland caused the development of a fatal cachexia; thus demonstrating that the gland had continued to perform its natural function in its new location.

Christiani has discovered accessory thyreoids in the neck of the rat; and Wölfler has found in man embryonal glandular tissue on the periphery of the thyreoid.

Out of fourteen rats operated upon by Lanz, for a special observation, thirteen died during the first two days after the operation with increasing difficulty in breathing, which Lanz is inclined to regard as due to a lesion of the recurrens, though he does not wish to contradict the conclusions of Christiani.

Since it has been demonstrated that rabbits and rats are especially susceptible, it is evident that the theory of Sanguirico and Orecchia, which has been elaborated by Horsley, that the food of the animal influences the outcome of thyreoidectomy, does not hold with all its original force. It is evident that the animals which have accessory thyreoids, whether they be carnivorous or herbivorous, withstand the operation best.

It must not be lost sight of that in rabbits the most minute particle of gland-tissue remaining suffices to perform the function necessary for the life of the animal; while, according to Fuhr's experiments, the dog perishes if more than two-thirds of the organ is removed. The omnivorous man can get along with a much smaller amount of thyreoid than this. It is a fact that certain articles of diet diminish the untoward symptoms after the operation. For example, a milk diet lessens the severity of the cachexia in dogs. Lanz assumes that the symptoms in cold-blooded animals are much less acute because of the slowness of their metabolism.

Vicarious Organs.—Since Zesas claimed that a compensatory hypertrophy of the spleen occurred after removal of the thyreoid, the idea has been much discussed. Albertoni and Tizzoni, and more recently Gley, have positively shown that the spleen has no vicarious function after extirpation of the thyreoid, and that the cachexia in an animal without a spleen did not appear any sooner than in a normal animal. Hofmeister found by his experiments on rabbits that the spleen and thymus were lighter after thyreoidectomy than in the control animals. De Quervain has observed the spleen in cases of cachexia thyreopriva, and has concluded that the spleen has no vicarious action in these cases. Besides this he has made the autopsy upon five persons dying of cachexia thyreoidectomica, and in four the size of the spleen was less than normal, in the fifth case it was normal.

Lanz did not see in any case an enlargement of the spleen, neither among his sharks nor thirty dogs operated upon, nor any of the animals with which he experimented.

Virchow has, contrary to the earlier view which held that the spleen, the thymus, and the thyreoid were analogous, declared that there is a parallelism between the tissue of the thyreoid, the cortical layer of the suprarenal capsule, and the hypophysis cerebri. In his teaching he has claimed that there are certain forms of tumors arising from these different tissues, and which he has designated as strumas,—struma suprarenalis, struma pituitaria.

Schiff has not been able to concur with the hypothesis that the suprarenal capsule can act vicariously for the thyreoid.

The changes in the hypophysis after thyreoidectomy were first observed by Rogowitsch.[1] He regarded the hypertrophy of the glandular portion of that body as due to an increase of functional activity. Streda [2] corroborated the observation of Rogowitsch. He invariably found enlargement of the hypophysis with enlargement and vacuole-formation in its parenchymatous cells. Neither of these observers noticed an increase in the formation of colloid material. Hofmeister observed in his rabbits an enlargement of the hypophysis, and a widening of the sella turcica. But few observations in man are recorded. The "myxœdema commission" found five cases of myxœdema without changes in the pituitary body. Bournville and Bricon [3] saw an hypertrophic hypophysis in a case of sporadic cretinism with absence of the thyreoid. Dolega [4] observed at the autopsy upon a cretin that the sella turcica was unusually long and deep, which he evidently erroneously attributed to a defective skull-formation.

The studies of the pituitary body in its relation to the thyreoid have not been productive of any very definite knowledge. The observations upon dogs have been unsatisfactory, for the reason that the animals have died so soon after the thyreoidectomy that the changes in the hypophysis could be observed only in their initial stages. Gley, Vassale, and Sacchi have attempted the removal of the latter body with poor success. Lanz implanted eight hypophyses during the course of several months in the peritoneum, in the tunica vaginalis testis, beneath the skin and peritoneum of a dog, and then removed the thyreoid. The cachexia ran its usual course, and the autopsy showed that all of the transplanted tissue had been absorbed. And so the relation between these two organs remains to be elucidated. That there is a relation may be inferred from their embryology. Dohrn has shown that the pituitary body is formed from the ectoderm, and he has observed in the same the remains of a branchial cleft. He has further shown that this gland in the petromyzon never becomes separated from the opening in which it is formed. It is thus checked in its development just as is the thyreoid gland of the same animal, of which it is unquestionably an analogue.

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[1] Ziegler's Beiträge, Bd. VI.

[2] Ziegler's Beiträge, Bd. VII.

[3] Archive de Névrologie, 1886.

[4] Ziegler's Beiträge, Bd. X.

Marie and Marineszo have called attention to the relation between the thyreoid and acromegaly. Sousa-Seithe has concluded on the ground of his study of acromegaly that atrophy of the thyreoid is more common than hypertrophy in that disease. According to him the only constant pathologico-anatomical change in acromegaly is a marked enlargement of the hypophysis. It is not impossible that the hypophysis possesses a function similar to that of the thyreoid, so that acromegaly—analogous to the myxœdema of cachexia thyreopriva—may be regarded as a cachexia pituitaria resulting from struma pituitaria.

The rôle of the thymus gland and its relation to the thyreoid is unknown. Marie has recently observed that the thymus is found hypertrophied in congenital myxœdema. In myxœdema in the adult, where the thymus should be greatly atrophied, it is found well developed. He has called attention to the persistence of the gland in acromegaly, and cites five cases of Basedow's disease, in all of which the thymus was enlarged.

There is a much closer relation between the thyreoid and the accessory thyreoid bodies than with any of these other structures, as Gley and Christiani have shown. Sandström and Gley have found that in rabbits these lateral thyreoid bodies are not connected with the gland proper. Christiani has found that this is not the case with other rodents. In the rat these bodies are enclosed within the thyreoid gland, but differ from the gland in that they still retain their embryonal structure and are separated from it by a sort of connective tissue capsule. In the mouse they show a tendency to separation, but are attached by one pole to the main gland; and in one variety (*arvicola arvalis*) this union exists only on the right side, while the left has no attachment to the central body. According to Gley's observations removal of the accessory bodies without the gland proper or removal of the latter without the former causes no cachexia. The extirpation of both structures was fatal, whether the operation was done in one or two stages. The removal of everything but one accessory thyreoid did not cause the death of the animal. The very small remaining nodule increased in size till at the end of one or two months it was double its original size and had acquired the structure of the adult thyreoid gland.

The Influence of the Food upon Thyreoid Cachexia.—Breisacher explains the fact that a milk diet lessens the cachexia by assuming that thereby the animal is kept in a state of imperfect nourishment. Lanz claims that poorly-nourished animals withstand the cachexia better than those that are well fed. The experiments of Munk and Fuhr have shown that the onset of the tetanic symptoms often follows the ingestion of animal food, and that under a milk diet the percentage of dogs which survive the operation is greatly increased. One-third or even a fifth of a lobe of the thyreoid, if left, suffices to prevent the cachexia in milk-fed dogs.

The Influence of Temperature.—Horsley found that by elevating the temperature, apes, after thyreoidectomy, could be kept alive 125 days; whereas in the ordinary room temperature they survived but twenty-four days. It has been observed that the human subject does much better in the warm hospital ward,—a fact which has been made use of in Kocher's clinic in a practical way.

Lanz has seen in short-haired dogs confined in cages so small as to prevent much movement, and in those which were not well dried after the operation, muscular convulsions similar to the initial spasms of tetany. He has seen similar convulsive movements in dogs which had been paralyzed by division of the spinal cord, and probably due to an inhibition of the heat-producing function. The chief source of the animal heat is in the muscles, and a "chill," caused by a more or less general muscular convulsion, has the tendency to elevate the bodily temperature. These convulsive movements alternating with polypnœa are the natural way of regulating the temperature in these animals. When they are kept in an atmosphere of high temperature the convulsions are much less marked.

The anatomical seat of tetany or the source of the muscular spasm has been investigated in Horsley's laboratory in London. In the first experiments the ischiatic nerve was divided either before the thyreoidectomy or after the spasms had begun. This prevented, in the four dogs thus operated upon, any spasms in the muscles supplied by the divided nerve; therefore, they were not of peripheral origin.

In order to find the relation of the spinal cord to this symptom, the cord was divided at the eighth dorsal vertebra in six animals. Five of these dogs were operated upon by thyreoidectomy either before or after this procedure, and one was reserved as a control animal. A sort of convulsive movement was observed in the hind legs of these animals, but altogether different from that which occurred in the front legs. Inasmuch as this same thing took place in the hind legs of the control animal, it was regarded as due to the spinal lesion. The cord of one dog was not divided till a convulsive action had begun in the hind legs, which ceased immediately on the division of the cord.

A third series of experiments were made upon five dogs. From these the motor area of one hemisphere was removed either before or after the thyreoidectomy. The thyreoid was left in one animal. In these cases the convulsions were more pronounced upon the corresponding side than upon the sound side. It was observed in two dogs that within two weeks after the cortical excision the symptoms of paralysis had entirely subsided, but immediately after the thyreoidectomy the paralysis reappeared and continued until the animal died of cachexia. Similar results were obtained by destroying the motor tracts of both hemispheres.

The cerebral nature of the cachectic changes is evidenced by the circumstance that shouting or otherwise exciting the psychic centres of the animal gives rise to muscular spasms. Furthermore, the initial restlessness and the subsequent apathy and stupidity of the animal, like the characteristic slowness of speech and impairment of intellect observed in man, must be due to cerebral disturbance.

A final series of experiments was performed by removing one hemisphere of the cerebellum. The spasms were greatly increased in the corresponding side of the body.

From these experiments it may be concluded that the tetania thyreopriva originates in the cord, but is influenced by the higher centres. Other bulbar symptoms appear in the course of these tetanic attacks, as dysphagia and vomiting; and death is probably due to a bulbar lesion,—*i.e.*, paralysis of the respiratory centres.

The clinical symptoms of the cachexia, as observed in the dog by Schiff, in the rabbit and rat by Gley and Christiani, in the cat by Von Eiselsberg, in the ape by Horsley, and in man by Kocher, represent all of our present knowledge upon the subject. Lanz adds that two dogs upon which he operated antiseptically died with much more acute symptoms than any upon which he operated aseptically.

Animals without thyreoids do not stand the narcosis as well as normal animals. Normal animals can always be resuscitated by artificial respiration, but these animals refuse to respond.

The symptomatology involves nervous disturbances of the (1) circulation; (2) respiration; (3) digestion; and (4) uro-genital functions.

There is a very pronounced diminution of the blood-pressure. Lanz found the blood-pressure in a dog to be 195 millimetres before the operation. After removal of the thyreoid it sank to 175 millimetres on the second day and to 135 millimetres on the sixth day. The pulse-curve showed no marked change except an increase in the frequency.

Leucocytosis and great increase in the number of blood-plaques were also often observed in cachectic dogs. De Quervain has counted the red blood-cells, and always found a diminution of about 25 per cent. in their number.

Albertoni and Tizzoni and Herzen have found a diminution in the oxygen and an increased venosity of the arterial blood; and the two former have concluded that the thyreoid has the function of fixing the oxygen in the red corpuscles. Vassale,[1] assuming that the red cells lost their oxygen-assimilating power after removal of the thyreoid, sought to restore it by injecting thyreoid extract into the circulation. In order to get at the process of oxidation more closely, Lanz made use of the methyl-blue experiment of Ehrlich. Three dogs without thyreoids and two normal dogs were killed with methyl-blue. The white blood-cells of the latter were much more stained than the former. The nuclei were very deeply stained, whereas in the former the white cells were not stained at all or had but a slight diffused stain.

Disturbances of respiration are always more or less marked. This is especially noticeable during the tetanic attacks in which the breathing becomes very rapid.

The digestive disorders are manifested by difficulty in swallowing, anorexia, and vomiting. The animal acts as though it were hungry and would like to eat, but fears the consequences of indulgence. The intestine is found at the autopsy to be dry and narrow.

Falkenberg reported to the German Congress for Internal Medicine, in 1891, the very frequent occurrence of sugar in the urine of dogs after thyreoidectomy. Neither this nor albuminuria are constant symptoms, and are probably of no specific importance.

The pronounced impairment of the genital functions in cretinism and cachexia thyreopriva is well known. Freund has studied for many years the relation of the thyreoid to the organs of generation, and has found that in cases of fibroma of the uterus and pregnancy the thyreoid becomes enlarged, and that labor causes a still greater enlargement, which disappears after twelve or twenty-four hours. The organ again becomes enlarged during lactation.

The elder Freund looked upon atrophy of the genitals as an etiological factor in Basedow's disease.

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[1] Centralb. für med. Wissensch., 1891, No. 1.

Lanz found that the spermatic fluid of a dog, very rich in active spermatozoa immediately before the operation, contained no movable sperms immediately after death.

Therapy of Thyreoid Cachexia.—St. Langer collected observations showing that boiling or decanting water removed the exciting cause of goitre. This points to the organic nature of the poison, and teaches that the well should be thoroughly protected from such pollution or should be closed and water brought from some other source. Where this is not possible reservoirs or cisterns should be employed, or the water should be boiled or filtered. On the other hand, since the disease destroys the function of the thyreoid, a right-sided goitre operation may be performed. In Dieffenbach's time the operation for goitre was not allowed. Velpeau and the Société de Chirurgie strongly condemned Roux for removing a goitrous thyreoid. These cases represent another surgical period. Kocher, having performed many hundreds of operations for goitre, declares the operation to be thoroughly safe. The demonstration that the total extirpation of the thyreoid gland is an unjustifiable operation has become an established law through the publications of Kocher and Reverdin.

Schiff's discovery that the injection into the circulation of thyreoid extract suffices to protect the animal from the cachexia thyreopriva has been successfully applied to man.

Kocher, in 1883, transplanted a piece of thyreoid beneath the skin, but observed that in the course of time it atrophied and disappeared. Bircher succeeded in improving a case of operative cachexia by thyreoid implantation. Encouraged by this, Kocher transplanted into the abdomen and beneath the peritoneum, but only obtained a temporary improvement. He also, in a case of cachexia thyreopriva and in a case of spontaneous cretinism (as a result of absence of the thyreoid), planted a freshly incised canine thyreoid in the tunica vaginalis testis and introduced a bit in the circulation in the femoral artery. The first case for a time was much improved; the second experiment was without result.

The implanted gland in these cases did not become permanently fixed, but was absorbed, and the therapeutic influence lasted only while the gland remained.

When the cause of the disease, the absence of the thyreoid, persists, its secretion must be supplied. At the last meeting of the British Medical Association, Horsley made the announcement that treatment would be more successful if the patients were first fed upon thyreoid gland and then grafted with fresh glandular tissue, in that the myxœdematous condition of the tissue would thereby be diminished and the transplanted material would more probably take root.

Murray and Howitz have found that in the non-operative cachexia (myxœdema) the patient's condition could be greatly improved by the injection of thyreoid extract.

Day by day reports of such cases come from England. The patients gain in flesh and strength, the myxœdematous swellings subside, and the stiffness, malaise, and apathy improve. The amount of urine increases, and much more urea is excreted.

Great caution is necessary in the injection of organic substances, because of the importance of their sterility. Cooked thyreoid fed by mouth still has a therapeutic action. This "substitution therapy," which has been found of unquestionable avail in disease of the thyreoid, may also be applied to other organs. The principle of its wide application was introduced into medicine by Brown-Séquard, in 1869, with the claim that all glands, with and without ducts, supplied some important substance to the blood.

The discovery of pancreas diabetes by V. Mering and Minkowsky supports the claim of Brown-Séquard of an "internal secretion" of the various glands; and Lanz holds it possible that other than glandular organs, besides their chief function, may possess other specific peculiarities of which we do not know; as, for example, that might explain Marie's "ostéo-arthropathie hypertrophiante d'origine pneumique." Brown-Séquard demonstrated that the kidney had another function than the excretion of urea by prolonging the lives of animals after double nephrectomy by injections of kidney extract. Similar experiments have been made with the spleen by Schiff and

Herzen. So with the liver: besides its digestive function by the agency of the gall, it plays a very important rôle in the metabolism of sugar and urea.

The pancreas and suprarenal capsules show a very close analogy to the thyreoid gland. Diabetes does not occur if a small portion of the pancreas is left remaining. Whether the implantation of a bit of pancreas will exercise a curative effect upon diabetes is an experiment greatly to be desired.

Though it is possible that Brown-Sèquard has placed too high a value upon the "liquide orchitique," still the experiences with the thyreoid tend to corroborate his philosophy. Like the thyreoid, removal of the testicle causes a specific cachexia, characterized by changes in the voice, imperfect growth of the hair, and a series of psychical changes.

The theory of Mendel that the loss of weight, and the increased amount of urea eliminated during the administration of thyreoid, will point to an increase of metabolism. In consideration that the absence of the thyreoid probably causes disturbances of the albuminous digestion,—*i.e.*, disturbances of the consumption of the tissue albumen,—it is certainly not unjustifiable to make careful experiments with thyreoid juice in other affections due to a diminution in the bodily metabolism. Anomalies in the disintegration of albumen, as, for example, adiposity, anæmia, gout, and other constitutional diseases, might be amenable to such treatment. Infantile tetany in the majority of cases is closely associated with rachitis; and respiratory spasms, convulsions, and other nervous disturbances are often observed in rachitis. Lanz would treat acromegaly with pituitary gland.

It has been observed by English physicians that the administration of thyreoid gland to healthy men, or the administration of too large doses in myxœdema, causes acceleration of the pulse, excitement, and dizziness. These facts throw some light upon the nervous manifestations in Basedow's disease, as being due to an exaggerated functional operation of the thyreoid gland.

Mendel found at the autopsy upon a case of morbus Basedowii that the left corpus restiforme was atrophic, and that there was also an atrophy of the solitary fasciculus on the right side. This observation is of importance, because the removal or incision of the corpora restiforma, practised by various experimenters upon the dog and rabbit, caused the appearance of Basedow's symptoms. On account of the relation of these pathological changes to the vagus centres, Mendel has regarded them as a physiological ground for locating the origin of the disease at this point. White found a case of Basedow's disease with hæmorrhage into the medulla, extending into the corpus restiforme. Contrary to these observations, Kocher and Möbius regard the disease as one primarily of the thyreoid. How otherwise can the numerous cures of the disease (Kocher, Lernke, Schnirer) by thyreoidectomy be accounted for, and the observation of Reynolds, that out of forty-eight cases but one occurred in a male? This corresponds with the sexual distribution of goitre on one side, and myxœdema on the other side.

Lanz's experiments upon himself do not confirm the experiences of the English physicians. He has frequently eaten fresh thyreoids, at one time as many as four at a sitting, without observing any quickening of the heart's action.

Before summing up the thyreoid question, a few examples may be cited from recent experiments to show its similarity to other organs.

Albanese has experimented with the suprarenal capsules in the laboratory of Mosso, and found that these organs have as their function the metamorphosis of toxic substances. Abelous and Langlois have found that in the summer time, when their function is greatly increased, the destruction of the capsules in the frog causes death in the first forty-eight hours, while in the winter the animals survive the operation thirteen days. If winter frogs are kept at a temperature of 22° C. after the operation, they live but three days instead of thirteen. Death is preceded by a constantly-increasing paralysis, which comes on much more rapidly when the animal is kept in motion. If one capsule and the larger part of the other are removed, the animal does not die.

Mering and Minkowsky have explained pancreatic diabetes by the theory that the pancreas supplies to the blood a substance which serves in the general metabolism by breaking up the carbohydrates. Lépine assumes that this substance is a ferment which acts upon sugar; that the pancreas produces a glycolytic ferment. He has observed that in diabetic blood the glycolytic ferment is diminished. Chvostek has found that in Basedow's disease the power of assimilating grape sugar is diminished.

The investigations of Schiff have shown that the liver protects the system from various poisons. It removes from the portal blood most of the alkaloids, copper salts, etc., but allows potash salts and other poisons to pass. Schröder has shown that the liver is the chief organ in which urea is formed; and Hahn, Massen, Nencki, and Pawlow have, by making the portal vein to empty into the inferior vena cava and thus diverting the liver circulation, found that animals so treated eliminate much more ammonia than normal, and that in the form of carbamic acid. Dreschel has shown that the oxidation of all organic nitrogenous compounds always results in the formation of carbamic acid; and that the liver is the organ in which this carbamic acid is converted into urea. The liver is not the only place where these changes occur, for the urine of dogs whose livers have been removed or the circulation of which has been shunted off is not free from urea. The symptoms in animals after such an operation are respiratory disturbances, psychical changes, somnolence, general weakness, clonic and tonic convulsions, coma, and death. These symptoms begin on the tenth day after the operation. Animals which do not eat flesh recover.

Considerable light is thrown upon the function of the thyreoid by the consideration of the cachexia thyreoidea, the "substitution therapy," the recent experimental studies of the functions of other glandular organs, and the limited chemical investigations.

One who has seen but once the acute form of cachexia thyreopriva in the dog cannot help believing that the removal of the thyreoid caused an acute intoxication in the animal. The emaciation of the animal is so rapid that it must not only be due to a diminution in the amount of food taken or assimilated, but to an increase of metabolism above the normal.

The differences in the symptoms of the more latent course of the cachexia in man, compared with the experimental tetany in animals, are partly due to the fact that in man the diseased gland is removed, and that during the period of the disease other organs have had time to gradually assume the function of the degenerating thyreoid. This chronic cachexia has been produced in apes by Horsley, in dogs by numerous experimenters, in rabbits by Hofmeister and Gley. The acute form has also been observed in man. Von Eiselsberg has reported twelve cases of tetany among the fifty-two total excisions of the thyreoid in Billroth's clinic; while among the 115 cases of partial excision tetany did not once occur.

A similarity is evident between the genuine tetany of man and the thyreoid tetany in the symptoms of œdema and trophic disturbances of the skin, hair, and nails. As an etiological factor in the true tetany are observed chiefly disturbance of digestion, as occur in gastro-intestinal affections. Ewald has reported a case in this line. The patient, who often suffered from attacks of tetany, could foretell such an onset, for always when after diarrhœa the stools became more consistent an attack occurred; and as soon as diarrhœa again developed the tetany disappeared. This can be simply explained by autointoxication, due to improper decomposition of the food. It is analogous to the eclampsia and convulsions of children due to digestive disturbances.

Since Schiff declared that the function of the thyreoid has no connection with its anatomical situation, many experiments to corroborate his views have been made. Fano and Zanda have repeated Munk's experiment of isolating the gland and ligating its vessels, with the unexpected result that the animals died of cachexia. These same authors have, on the other hand, disproved the hypothesis of Albertoni and Tizzoni that the thyreoid renders the red blood-cells capable of retaining oxygen, for they found that by diminishing the latter no symptoms of cachexia were produced. The question whether the gland supplies some material which is essential for nourishment in the animal economy, or whether it destroys certain poisonous materials in the blood, has been decided by Schiff in favor of the latter.

The following facts corroborate this view: Colzi transfused cachectic dogs with blood from healthy dogs, and observed that the animals acted perfectly normally for two or three days thereafter, and then relapsed into their abnormal state. Fano, Zanda, and Rogowitsch have found by transfusion of blood and salt solution from normal to cachectic animals and *vice versa* that, in the first instance, improvement of the tetanic symptoms followed, and in the last a rapid increase of the symptoms resulted. Alonzo and Laulanié[1] have found an increase in the virulence of the urine after thyreoidectomy. Excepting in cases of temporary suppression of the tetanic attacks by the injection of thyreoid juice, Gley and Alonzo have observed that the poisonous properties of the urine of dogs after thyreoidectomy is much greater than the normal, and is especially marked on the second or third day after the first appearance of the symptoms. A toxic material, therefore, enters the urine after removal of the thyreoid. Gley has shown that this material circulates in the blood by injecting the blood-serum of these animals, and producing spasms which cannot be produced by the injection of normal serum. Breisacher fed his dogs alternately with milk, raw meat, cooked meat, and bouillon. Under a diet of milk and cooked meat the tetanic symptoms were least marked. The raw meat and bouillon caused an increase in the symptoms. When the operation was done in two stages, the animals died much quicker under a meat diet than under a milk diet. It is evident that the substances in meat which give rise to the toxine are soluble in water.

When we now come to study the working of the poison which is thus eliminated by the glandula thyreoidea, it is evident that it must be a so-called "nervous poison," and that the conclusions of Schiff and Horsley have been well grounded.

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[1] Comptes rendus de la Soc. de Biolog., 1891, 43.

Abelous and Langlois have found by experiment that the toxic principle in the blood of the animal, after removal of the suprarenal capsules, acts on the motor-nerve endings very much like curare; and Lanz elicited from his animals by percussing the chest attacks resembling those of strychnine-poisoning. The itching of the skin, of which the animals after thyreoidectomy often suffered, seemed to be analogous to that in jaundice due to cholæmia.

The results of therapy still add something to our knowledge of the function of the thyreoid. The circumstance that the exhibition of pilocarpine causes an improvement in myxœdema is doubtless due to the elimination of toxic materials through the increased perspiration and salivation.

When the field of physiological chemistry is explored for information as to the function of the thyreoid, the following facts are found:

It is possible for abnormal albuminous decomposition to take place in the intestine, which causes an auto-intoxication indicated by the presence of indican in the urine.

The symptoms of oxaluria are weakness and mental debility, which, according to Centani, are cured by a steady diet of meat.

In our bodies is lecithin, which contains cholin, an entirely harmless substance, but which by the extraction of a molecule of water is converted into neurin, a poisonous compound, and which by the loss of still more water becomes changed into cadaverin and putrein, two exceedingly poisonous substances. Normally, however, cholin is broken up into non-poisonous compounds.

Araki has observed that well-fed animals which are kept in an atmosphere poor in oxygen develop lactic acid, glycose, and albumen in the urine. If the animal is kept hungry, the glycose is not present with the other two substances.

The presence of lactic acid in the muscles in *rigor mortis* and tetanus explains the hypothesis of Marcuse that in muscles an unknown albuminous body exists, from which lactic acid is formed during normal activity or by the death spasm, either directly or through the intermediary formation of glucose.

Colasanti and Moscatelli have found paralactic acid in the urine of soldiers after long marches.

As a chemical ingredient of the thyreoid gland Bubnow found no mucin in the watery extract, but it gave the reaction of albumen, besides which were also present cretinin, hypoxanthin, guanin, and lactic acid, all of which were qualitatively determined. The lactic acid has been repeatedly found in the form of paralactic acid.

Horsley has, on the ground of the increased amount of mucin in the tissues of cases of thyreopriva, regarded the thyreoid as the seat of the metamorphosis of mucinoid substances; and Rogowitsch has drawn a parallel between myxœdema and amyloid degeneration, which is caused by the formation in the blood of some unknown poisonous substance which finds its way into the blood as a result of chronic suppuration.

In his elaborate treatise, Lanz has thus summed up the thyreoid question. There is much material for speculation in the analogy between the function of this gland and that of many other organs of the body, the accurate determination of which rest largely with physiological chemistry. It is certain that the surgery of the thyreoid has witnessed marked changes in the last two decades; and the vast amount of material in this line which has been accessible to Kocher has made his name especially prominent in this particular field of surgery.

JAMES P. WARBASSE.

THORBURN ON THE SURGERY OF THE SPINAL CORD AND ITS APPENDAGES.[1]

THE author begins by discussing the propriety of the use of the term "laminectomy." Though acknowledging its bastard derivation,

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[1] Abstract of lectures delivered before the Royal College of Surgeons of England, by William Thorburn, M.D., F.R.C.S., of Manchester, British Medical Journal, June 23 and 30, 1894.